II. REMARKS

Claims 1-19 and 21 and 25-30 were pending in the parent application. Claims 1-18 have been withdrawn pursuant to a restriction requirement and claims 20, 23 and 24 have been canceled. Claims 19, 21 and 25-30 were variously rejected under 35 U.S.C. §§ 112, first and second paragraphs.

Applicants acknowledge with appreciation withdrawal of the all the former 102 and 103 rejections.

To expedite prosecution, claim 19 has been amended herein to eliminate repetition of the term "toxin." Claim 21 has been canceled. New claims 31 to 43 have been added. Support for the new claims can be found throughout the specification as filed, for example as shown in the following table.

Claim	Exemplary Support
31	page 16, lines 22-31
32	page 16, line 31 to page 19, line 14
33	page 18, line 10
34	page 18, line 4
35	page 18, line 9
36 to 43	page 19, lines 14-23

Applicants reserve the right to file a continuation or divisional application directed to the subject matter of previous claims at any time during the pendency of this application.

Drawings

The Examiner notes that formal drawings have not yet been received. Applicants submit herewith a revised Figure 2, thereby obviating this objection.

35 U.S.C. § 132

The Examiner has objected to the new Figure 3 and the revised Sequence Listing containing SEQ ID NO:5. In support of these new matter rejections, the Office Action alleges, that neither the specification nor the original claims provide descriptive support for the amendments. (Office Action, page 4).

Applicants submit that neither the Sequence Listing nor Figure 3 included new matter and, accordingly, request the objection be withdrawn.

The proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an applicant from adding information that goes beyond the subject matter originally filed. See, *e.g., In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981) and MPEP § 2163.06. Further, the claims as filed in the original specification are part of the disclosure. Therefore, if an application as originally filed contains a claim disclosing material not found in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. *See, e.g., In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985).

In the pending case, the alleged "added" information does not in any way go beyond the subject matter originally filed. Applicants note that, at the time of filing, the sequence presented in Figure 3 was publicly available on GenBank (as published in Domenighini et al. (1995) *Mol. Microbiology* 15(6):1165-1167). Moreover, the originally filed application specifically discloses a sequence of LT (Figure 1A and B), which, like added Figure 3, contains an alanine at residue 72. In addition, the originally filed claims also specifically referred to the Ala-72 residue of the original figures. Therefore, Applicants are merely presenting an additional LT sequence based on information that was publicly available at the time of filing. Indeed, to the extent that there are differences between the sequences presented originally and those in Figure 3, it is well known that sequencing errors are a common problem in molecular biology. See, e.g., Peter Richterich, Estimation of Errors in 'Raw' DNA Sequences: A Validation Study, 8 Genome Research 251-59 (1998) and Domenighini et al, *supra*. Any discrepancies in sequence between original Figure 1 and added Figure 3 fall under the category of "minor errors" and do not rise to the level of new matter. As noted above, the pre-filing date existence of the GenBank entry also indicates that this is not an instance in which a deposit was made after the filing date of the application.

Thus, there is nothing in the previous amendments that goes beyond the originally filed subject matter and, accordingly, new matter has not been added. Therefore, Applicants request that this objection be withdrawn.

35 U.S.C. § 112, First Paragraph, Enablement

The Examiner alleges that the specification fails to enable that the mutant LT-R72 used in the claimed methods is detoxified. (Office Action, page 5). In particular, the Examiner states, in part:

> In the instant case, although the construction and evaluation as an adjuvant of LT-R72 is described in the specification, the state of the art suggests than an LT mutant having a site directed substitution of alanine to arginine at position 72 is not "detoxified" as claimed currently. For instance, Pizza [citation omitted] taught such a mutant ... Pizza et al. stated that this mutant was fully toxic ....

> Similarly, Figures 4 and 5 of WO 98/18928 ... clearly show that LT-R72 mutant is not detoxified. Office Action, paragraph bridging pages 5-6.

Because the specification fully enables methods using detoxified LT-R72 mutants, Applicants traverse the rejection.

The test of enablement is whether one of skill in the art could make and use the invention based on the specification as a whole. A specification must be taken as enabling in the absence of evidence to the contrary. The courts have consistently held that not every last detail of any invention need be described, "else patent specifications would turn into production specifications, which they were never intended to be." See, e.g., *In re Gay*, 309 F.2d 769, 774 135 USPQ 311, 316 (CCPA 1962) and *Staehelin v. Secher* 24 USPQ2d 1513, 1516 (BPAI 1992). Further, working examples are never required in order to establish enablement. MPEP 2164.02. In sum, the standard for determining enablement is not what the references allegedly predict, but, rather, what Applicants' specification (in view of information known in the art) actually teaches one of skill in the art.

The specification as filed clearly establishes one of skill in the art could practice the claimed methods without undue experimentation following the guidance set forth in the specification as filed. Contrary to the statements made in the Office Action, the specification provides significant guidance as to the source and characteristics (including toxicity as compared to wild-type) of the **actual** LT-R72 mutant used in the Examples. In fact, Example 5 is clear that the detoxified LT-R72 mutant used in the claimed methods was obtained as described in Giuliani et al. (1998) *J. Exp. Med.* 187:1123-1132 (a copy of which is attached hereto for the Examiner's convenience). Giuliani's LT-R72 is unmistakably "detoxified," as defined in the specification on page 7, line 27 through page 8, line 8. (See, text on page 1125 of Giuliani, right column and Figure 1D comparing toxicity of wild-type LT and LT-R72 in Y1 cell assays). Thus, the specification plainly teaches that LT-R72 mutants used in the claimed methods are detoxified and, accordingly, fully enables these claims.

Furthermore, in view of the teachings of the specification (including Giuliani), Applicants submit that the Office's reliance on Pizza and/or WO 98/18928 is misplaced. The state of the art is judged at the time the application was filed. Both Pizza and WO 98/18928 describe work done before Giuliani and others discovered that LT-R72 was, in fact, detoxified and before Applicants discovered that LT-R72 functions as a parenteral adjuvant. Therefore, these references are not reasonably indicative of the state of the art at the time of filing. Nor do Pizza and WO 98/18928 outweigh what is actually disclosed in the specification regarding the claimed methods and the definitively detoxified molecules used in those methods. Simply put,

the references cited by the Examiner have absolutely no bearing on whether the specification as filed enables the pending claims.

In the pending case, the Office has not shown, with evidence, reasons as to why the specification is not enabling. Accordingly, a *prima facie* case of non-enablement has not been established and withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claim 19 stands rejected as allegedly confusing in its double recitation of the term "toxin." (Office Action, page 5). Claim 19 has been amended to remove the first occurrence of the term "toxin," thereby obviating this rejection. In view of the foregoing amendments, Applicants respectfully request that this rejection be withdrawn.

III. CONCLUSION

In view of the foregoing amendments and the Office's acknowledgment that the amended claims define an invention that is free of the prior art as well as described and enabled by the specification, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Please direct all further communications regarding this application to:

Rebecca M. Hale, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097.

Respectfully submitted,

Date: 21 April 03

By: _____
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: 510-923-3179
Facsimile: 510-655-3542

Version Showing Changes Made to Claims

19. (Twice Amended) A method for immunizing a vertebrate subject against at least one selected antigen, the method comprising the step of parenterally administering to the vertebrate subject an immunologically effective amount of

a) a parenteral adjuvant comprising a detoxified mutant of an *E. coli* heat-labile [toxin] (LT) ADP-ribosylating toxin in combination with a pharmaceutically acceptable vehicle, wherein said detoxified mutant is LT-R72; and

b) at least one selected antigen.

Claim 21 has been canceled, without prejudice or disclaimer.

31. (New) The method of claim 19, wherein said antigen is a viral antigen.

32. (New) The method of claim 31, wherein said viral antigen is selected from the group consisting of an influenza antigen, an HSV antigen, an HIV antigen, a CMV antigen, an HCV antigen, an HDV antigen, a poliovirus antigen, an HAV antigen, an EBV antigen, a VZV antigen, and a RSV antigen.

33. (New) The method of claim 32, wherein said viral antigen is an influenza virus antigen.

34. (New) The method of claim 32, wherein said viral antigen is a poliovirus antigen.

35. (New) The method of claim 32, wherein said viral antigen is a RSV antigen.

36. (New) The method of claim 31, wherein said antigen is a bacterial antigen.

37. (New) The method of claim 36, wherein said bacterial antigen is selected from the group consisting of *Bordetella pertussis* antigens, *Helicobacter pylori* antigens, streptococcal antigens, meningococcus A antigens, meningococcus B antigens, and meningococcus C antigens.

38. (New) The method of claim 37, wherein said bacterial antigen is a *Bordetella pertussis* antigen.

39. (New) The method of claim 37, wherein said bacterial antigen is an *Helicobacter pylori* antigen.

40. (New) The method of claim 37, wherein said bacterial antigen is a streptococcal antigen.

41. (New) The method of claim 37, wherein said bacterial antigen is a meningoccus A antigen.

42. (New) The method of claim 37, wherein said bacterial antigen is a meningoccus B antigen.

43. (New) The method of claim 37, wherein said bacterial antigen is a meningoccus C antigen.

Currently Pending Claims

19. (Twice Amended) A method for immunizing a vertebrate subject against at least one selected antigen, the method comprising the step of parenterally administering to the vertebrate subject an immunologically effective amount of

a) a parenteral adjuvant comprising a detoxified mutant of an *E. coli* heat-labile (LT) ADP-ribosylating toxin in combination with a pharmaceutically acceptable vehicle, wherein said detoxified mutant is LT-R72; and

b) at least one selected antigen.

20. to 24. Canceled.

25. (Amended) A method according to claim 19, wherein the adjuvant and the antigen are administered subcutaneously, transcutaneously or intramuscularly.

26. A method according to claim 19, wherein the pharmaceutically acceptable vehicle is a topical vehicle.

27. A method according to claim 26, wherein the adjuvant and the antigen are administered transcutaneously.

28. A method according to claim 19, wherein the adjuvant is administered to the vertebrate subject prior to administering the selected antigen.

29. A method according to claim 19, wherein the adjuvant is administered to the vertebrate subject subsequent to administering the selected antigen.

30. A method according to claim 19, wherein the antigen is administered to the vertebrate subject concurrent with administering the selected antigen.

31. (New) The method of claim 19, wherein said antigen is a viral antigen.

32. (New) The method of claim 31, wherein said viral antigen is selected from the group consisting of an influenza antigen, an HSV antigen, an HIV antigen, a CMV antigen, an HCV antigen, an HDV antigen, a poliovirus antigen, an HAV antigen, an EBV antigen, a VZV antigen, and a RSV antigen.

33. (New) The method of claim 32, wherein said viral antigen is an influenza virus antigen.

34. (New) The method of claim 32, wherein said viral antigen is a poliovirus antigen.

35. (New) The method of claim 32, wherein said viral antigen is a RSV antigen.

36. (New) The method of claim 31, wherein said antigen is a bacterial antigen.

37. (New) The method of claim 36, wherein said bacterial antigen is selected from the group consisting of *Bordetella pertussis* antigens, *Helicobacter pylori* antigens, streptococcal antigens, meningococcus A antigens, meningococcus B antigens, and meningococcus C antigens.

38. (New) The method of claim 37, wherein said bacterial antigen is a *Bordetella pertussis* antigen.

39. (New) The method of claim 37, wherein said bacterial antigen is an *Helicobacter pylori* antigen.

40. (New) The method of claim 37, wherein said bacterial antigen is a streptococcal antigen.

41. (New) The method of claim 37, wherein said bacterial antigen is a meningoccus A antigen.

42. (New) The method of claim 37, wherein said bacterial antigen is a meningoccus B antigen.

43. (New) The method of claim 37, wherein said bacterial antigen is a meningoccus C antigen.